The Examiner has rejected claims 1,2, 7, and 8 as allegedly anticipated by Bizzini et al. (US Patent No. 4,594,336). Applicant respectfully requests reconsideration and withdrawal of this rejection.

Claim 1 is drawn to a modified toxin comprising an inactive Clostridial neurotoxin and a drug or other bioactive molecule attached thereto, wherein the neurotoxin is internalizable by the cell. Claim 7 is directed to a pharmaceutical composition comprising an inactive Clostridial toxin having specific binding affinity for a target nerve cell, a drug or other bioactive molecule attached thereto, and an excipient, wherein the neurotoxin is internalizable by the target nerve cell. Claims 2 and 8 depend from these claims, respectively.

Bizzini is directed to the use of a thiolated polypeptide consisting of the B-II_b fragment of tetanus toxin that retains the properties of retrograde transport and ganglioside and synaptic membrane binding of the unthiolated fragment.

In order for a reference to anticipate a patent claim, the reference must literally disclose each and every element of the claimed invention. See e.g., Kalman v. Kimberly-Clark Corp., 218 USPQ 781, 789 (Fed. Cir. 1983) In the present situation, there is no disclosure of "clostridial neurotoxin" in Bizzini; rather Bizzini's disclosure is limited to a single Clostridial neurotoxin: tetanus toxin. That this is true can be seen by the recitation of the property of retrograde axonal transport, which is not a property of other Clostridial toxins such as botulinum toxin. Thus, independent claims 1 and 7 (and therefore claims 2 and 8) contain an element not found in Bizzini: clostridial toxins other than tetanus toxin. As such, Bizzini cannot properly be said to anticipate the present claims

For this reason, Applicant respectfully requests reconsideration and withdrawal of this ground of rejection.

Rejections Pursuant to 35 USC §102(e)

Claims 1, 2, 7, 24, and 25 were rejected as allegedly anticipated by Mond et al. (US Patent No. 5,585,100). Applicant respectfully traverses this rejection.

Independent claims 1 and 7 have been described above. Claim 24 depends from claim 1. Claim 24 is directed to a method for treating a mammal having acute botulinum toxin poisoning comprising treating the mammal with an inactive clostridial toxin.

Mond describes constructs for improved vaccines having increased immunogenicity. One such

construct comprises conjugation of *H. influenzae* PRP (polyribosyl-ribitol-phosphate) with a tetanus toxoid.

Unlike the pending claims, there is no disclosure of internalization of the Mond conjugate; in fact, the whole idea of the conjugate of the Mond disclosure is to recruit T cells in the extracellular environment. Additionally, as with Bizzini, there is no disclosure of clostridial toxins other than tetanus toxin. There is no disclosure in Mond of anything like the method of claim 25 for the therapeutic competitive inhibition of botulinum toxin in a mammal suffering from acute poisoning.

Thus, Mond does not disclose each and every element of any of the indicated claims as required by Section 102 to show anticipation. Applicant therefore respectfully requests reconsideration and withdrawal of the rejection.

Claims 1,2,7,8, and 22-24 were rejected as allegedly anticipated by Johnson or Halpern. Applicant respectfully traverses this rejection.

Claims 1,2,7,8 and 24 have been described above. Claims 22 and 23 depend from claim 1.

Johnson (US Patent No. 5,696,077) is concerned with stabilized preparations comprising active botulinum type B neurotoxin complex. This complex contains non-toxin botulinum proteins together with the active type B toxin, as the Examiner has pointed out in column 2, lines 42-67.

The present claims are concerned with inactive clostridial neurotoxin (as contrasted with a complex containing active neurotoxin with non-toxin components). Therefore, Johnson cannot properly be said to have disclosed every element of (anticipate) any of the rejected claims.

Halpern (International Patent Publication No. WO94/00487) is concerned with the preparation of an immunogen against tetanus toxin. The disclosure is limited to the use of a fragment of tetanus toxin and is concerned with preparation of a vaccine; a "carrier" (adjuvant) is used to permit a greater immunogenic response. As with Mond, above, internalization of an inactive toxin molecule linked to a drug is not taught, as vaccines must be available extracellularly for T cell activation. Therefore every element of the rejected claims has not been found in the applied reference, and the reference cannot anticipate.

For this reason, Applicant respectfully maintains that the rejection has been overcome requests that this ground of rejection be withdrawn.

Rejection Pursuant to 35 USC §103(a)

Claims 3 and 4 have been rejected as allegedly obvious over Bizzini in view of Fraenkel-Conrat et al. Applicant respectfully traverses this rejection.

Claims 3 and 4 depend from claim 1; claim 3 specifies that the modified clostridial toxin is inactivated by an amino acid change in its light chain and claim 4 specifies that the modified toxin is selected from the group of either tetanus or botulinum toxins comprising specified amino acid changes.

As indicated above, Bizzini is concerned with use of a thiolated polypeptide consisting of the B-II_b fragment (a of tetanus toxin that retains the properties of retrograde transport and ganglioside and synaptic membrane binding of the unthiolated fragment. See Bizzini, column 3, lines 15-44.

By contrast, the invention of claims 3 and 4 involves an inactive clostridial toxin. As indicated in the specification on page 6, the invention concerns both the heavy and the light chain of the toxin, as both are required for optimal receptor-ligand interaction. The light chain is attenuated to make the molecule non-toxic. Thiolation of the toxin is not disclosed or claimed. Thus, the claimed invention is not a proteolytic fragment of the toxin, but comprises both heavy and light chains, as indicated in the specification. There is no suggestion of this in Bizzini.

Additionally, claim 3 and claim 4 include toxins that do not undergo intraneuronal retrograde transport; botulinum toxin is localized at the axonal presynaptic junction, rather than traveling towards the cell body or dendrites. Bizzini discloses that the toxin fragment must undergo retrograde transport. Additionally, Bizzini indicates that the drug must have NH_2 groups in order to link to the thiolated toxin fragment. (See e.g., col. 6, line 21-22). There is no such restriction in the present case. (See specification, page 15, lines 20-21).

Bizzini therefore not only fails to suggest, but actually teaches away from the invention of claims 3 and 4.

Finally, Fraenkel-Conrat discloses amino acid substitutions of the tetanus toxin light chain that can render it non-toxic. However, there is no suggestion of a method for drug delivery using the method of claims 3 and 4. The addition of this reference to Bizzini cannot cure the deficiencies of the latter; the combination of these references does not render claims 3 and 4 obvious. There is no indication in Bizzini of where residues 234 of the tetanus toxin light chain might be in fragment BII_b, or even whether such residues are present in this fragment at all. As indicated, there is no suggestion of botulinum toxin at all.

For the foregoing reasons, Applicant submits that the claims are in condition for allowance, and respectfully requests that the Examiner issue a Notice to that effect. A Petition for a one-month extension of time accompanies this communication. Should any fee be due in connection with this communication, the Commissioner is authorized to use Deposit Account No. 01-0885 for the payment of such fees, or to credit any overpayment. The Examiner is invited to contact the undersigned at the indicated telephone or facsimile number it would be thought helpful in advancing the prosecution of this application.

Respectfully submitted,

Carlos A. Fisher
Registration No. 36,510
ALLERGAN
Telephone: 714-246-4920
Fax: 714-246-4249